



Huntington's Disease
Society of America

THE MARKER

2019 RESEARCH REPORT



Dr. Edward Wild



Dr. Jeff Carroll



Dr. Marcy MacDonald



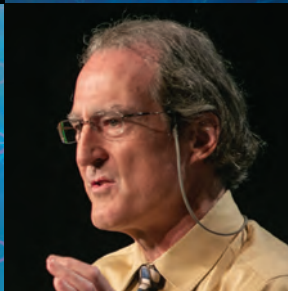
Dr. Neil Aronin



Dr. Jang-Ho Cha



Dr. Anastasia Khvorova



Dr. Craig Mello

Pioneers in HD Research Share
Their Findings at the 34th Annual
HDSA Convention in Boston.

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GREATER GOALS



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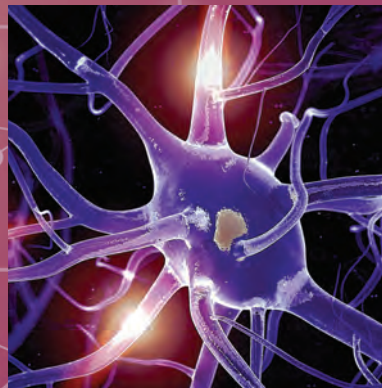
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To Keep our HD Momentum Going, We Must Have Even Greater Goals

In last year's HDSA Research Report, I stated, "I know that the HD families around the world will be ready to answer the call for brave research volunteers to get disease-modifying trials completed... quickly." However, I could not have predicted just how quickly!

After years of waiting, the community was rewarded with a spree of new potentially disease-modifying clinical trials. With such anticipation and demand for these studies, I guess it should not come as a surprise that the Natural History and GENERATION- HD1 studies from Roche-Genentech, the Precision HD2 trial from Wave Life Sciences and the Signal study from Vaccinex all completed US recruitment in 2019. It was just last year, at the HDSA Convention in Los Angeles, that the Roche team stood on stage to announce that the first ever Phase 3 clinical trial to test a huntingtin-lowering drug would begin in 2019.

While we await results from these studies, the field continues to keep the momentum going. This year saw uniQure begin the first ever gene therapy trial for HD. Recent clinical successes in gene therapy for spinal muscular atrophy (SMA) provide a sense of optimism that perhaps this approach could alter the course of HD as well. Novartis also announced plans to launch a Phase 2 trial to investigate an orally administered drug to lower huntingtin.

The community excitement was exemplified with a record number of people (1,225) attending the 34th Annual HDSA Convention in Boston, MA. Attendees were treated to a presentation by Dr. Craig Mello, Nobel Laureate and discoverer of the science that has enabled huntingtin lowering trials to become a reality. Dr. Mello and his colleagues announced the formation of a new company that will try to treat HD. This is one of dozens now currently pursuing HD as a primary indication in their business plan.

As I look back on 2019, I am inspired by the progress that has been made by the HD research community. While the light of hope now shines brighter for all of us, much work remains before HD becomes a thing of the past. The scientific progress of this past year give me confidence that 2020 will bring generations of HD families one step closer to relief. I hope that you enjoy reading about the progress in this year's *The Marker*.

Thank you for all you do!

George Yohrling, PhD

HDSA Senior Director, Mission & Scientific Affairs

2019 Human Biology Project Fellowships

In October of 2019, HDSA awarded five grants under the Society's largest research initiative, the HDSA Huntington's Disease Human Biology Project. These grants, totaling \$575,000, represent HDSA's patient-centric research focus which brings basic and clinical researchers together to facilitate

Huntington's disease science in the human condition. Applicants worldwide proposed projects addressing HD through small clinical studies or donated human samples. This year's winners hail from Scotland, Spain, and the United States.



Danielle Larson, MD
*Northwestern University
Feinberg School of Medicine*

Dr. Larson will study whether remote "telemedicine" visits with a neurologist could be just as helpful as in-person visits for an HD patient or family.



Osama Al Dalahmah, MD
Columbia University

Dr. Al Dalahmah will examine how astrocytes, the brain's support cells, change over the course of HD to become harmful versus helpful.



Vilija Lomeikaite, PhD candidate
University of Glasgow

Vilija will work on improving the existing methods to detect an increase in CAG repeats in certain cells of the body and brain during the course of HD.



Ricardo Mouro-Pinto, PhD
*Massachusetts General Hospital
and Harvard Medical School*

Dr. Mouro-Pinto will focus on the biology of CAG repeat expansion in hopes of developing drugs to stop this process.



Saul Martinez-Horta, MsC,
Sant Pau Hospital, Barcelona

Saul will examine what kinds of changes are happening in the brain and blood when HD patients begin to have difficulty with planning and memory.



Highlights from Previous HD Human Biology Project Fellowships

Madeleine Sharp, MD

*2016 Human Biology Fellow,
Postdoctoral Research Fellow,
McGill University*

The overall goal of Madeleine's project was to uncover the mechanisms underlying common cognitive and behavioral symptoms of HD. She designed tasks to detect subtle changes in learning and memory, even in pre-symptomatic carriers of the HD gene. She exceeded her enrollment goals with a total of 79 HD patients, some of whom were recruited at HDSA's National Convention. This work is impactful from the perspective of early diagnostics as well as potential interventions. Certain cognitive tasks shown to create long-lasting improvements in memory and reward processing could potentially be powerful and safe approaches to treating early changes in thinking.



Marina Papoutsis, PhD

*2017 Human Biology Fellow,
Postdoctoral Researcher,
University College London*

Marina is a skilled statistician whose project focused on the concept of "cognitive reserve," the idea that intelligence, education, or an intellectually stimulating lifestyle can be protective or delay cognitive problems for people with the HD gene. In 2019 she completed an analysis showing that HD patients with higher levels of education or a higher IQ had a slower rate of decline in mental abilities. This knowledge could be applied to design stimulating interventions, encourage young people in HD families to follow intellectual pursuits, or to stratify patients in clinical trials.



Richard Hickman, MD

*2018 Human Biology Fellow,
Neuropathology Fellow,
Columbia University*

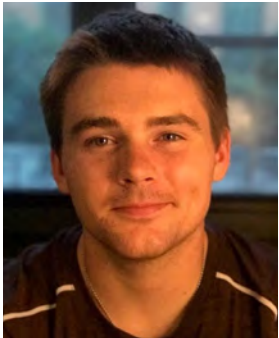
Richard's HDSA funding is allowing him to work closely with Dr. Jean-Paul Vonsattel to learn the art of HD brain banking, an invaluable skill that enables researchers to use donated human brain tissue. His HDSA fellowship also helped him to transition to an assistant faculty position at Columbia University. He is working with autophagy expert Dr. Ai Yamamoto to explore how the brain's waste disposal systems handle toxic huntingtin protein. Beyond potential discoveries that could help harness the power of the cell's clean-up crew to combat HD, the skills required to make use of precious brain donations from HD families are highly sought after.



2019 Donald A. King Summer Research Fellowships

In April of 2019, four exceptional undergraduate students were awarded HDSA's Donald A. King Summer Research Fellowships. These awards are named in honor of Donald King, who served as HDSA Board Chairman from 1999 to 2003 and worked tirelessly to advocate for HD families until his death in 2004. In order to further meaningful discoveries about Huntington's disease and ensure that bright young scientists are steered towards the

field, this program supports undergraduates who have committed their summers to training in an HD research lab. Applications are accepted between December and March each year and are reviewed by HDSA's Scientific Advisory Board. The 2019 Donald A. King Summer Research Fellows completed focused HD research projects under the supervision of senior scientists.



Zach Cook

Brown University

Zach spent the summer working with Dr. Marc Tatar, testing effectiveness of drugs in a fruit fly (*Drosophila*) model of Huntington's disease.



Chloe LaRochelle

University of Central Florida

Chloe worked under the guidance of Dr. Amber Southwell on a project investigating aggression in HD mice.



Alexandra Putka

Duke University

Alexandra worked in the laboratory of Dr. Audrey Dickey to elucidate how altered function of a protein called PPAR contributes to HD pathology.



Colleen Strohlein

University of Pittsburgh

Colleen spent the summer working in the laboratory of Dr. Robert Friedlander, to investigate whether phosphorylation of huntingtin protein affects its localization to mitochondria.

2019 Berman-Topper Family HD Career Development Fellowships

As part of HDSA's commitment to developing the next generation of passionate and innovative Huntington's disease scientists, the Berman-Topper Family HD Career Development Fellowships provide up to \$80,000 of funding per year for three years to young scientists and clinicians who desire to make HD part of their long-term career plan. These prestigious awards are made possible due to the generosity of the Berman and Topper families and CHDI Foundation. HDSA's Scientific Advisory Board reviewed applications from researchers from all around the world, and HDSA was able to award two scientists the 2019 Berman-Topper Fellowship — **Dr. Lauren Byrne** and **Dr. Nicholas Caron**.

Dr. Byrne is working under the guidance of Dr. Ed Wild at University College London. Her project will better prepare the field for future disease prevention studies by researching how early in life we can detect changes in the neurofilament light (NfL) protein in persons with the HD mutation.

Dr. Caron is guided by Dr. Michael Hayden at the University of British Columbia. He will investigate novel ways to enhance the delivery of huntingtin lowering antisense oligonucleotides across the blood-brain barrier.



Dr. Nicholas Caron

*Dr. Lauren Byrne and mentor
Dr. Ed Wild at HDSA's
Convention in Boston.*



HD Trialfinder

In 2015, to facilitate participation in clinical trials for both families and researchers, HDSA created **HD Trialfinder**, a clinical trials matching service. It's a way for individuals with Huntington's disease, caregivers, healthy volunteers, and physicians to connect with current research studies. HD Trialfinder includes an easy-to-use website and free call center staffed by trained HD clinical trial navigators.

Through involvement in the worldwide HD research community, HDSA keeps track of national, international, and local clinical trials so that the



HD Trialfinder listing stays up-to-date with studies that need participants. Anyone can visit the website to read about ongoing studies, and by creating a profile for themselves, a loved one, or a patient, users can find out which nearby studies they are eligible for, and locate contact information to get involved directly. 2019 saw a record number of HD Trialfinder users, with more than 6,000 profiles, contributing to the speedy U.S. recruitment of three huntingtin-lowering trials.

Visit www.hdtrialfinder.org or call 1-866-890-6612 to learn more.



Clinical Trial Updates

Clinical Trial Updates

ENROLL-HD

Enroll-HD Evolving to Meet Future Clinical Trial and Researcher Demands

Enroll-HD is an observational study that is just one component of the entire Enroll-HD research platform that serves to enable all future HD clinical studies. Enroll-HD is sponsored and managed by **CHDI Foundation**, a not-for-profit biomedical research organization dedicated to rapidly developing therapies that slow the progression of Huntington’s disease.

The ultimate goal of HD researchers is to prevent HD gene expansion carriers from ever getting sick. To do so, pre-symptomatic clinical trials will be required. To make this goal a reality, the new Enroll-HD recruitment strategy is focusing on the



recruitment of at risk, pre-manifest and early stage participants. As of November 1, 2019,

there are 18,845 active participants enrolled at 158 active sites in 19 countries around the world.

The revised recruitment strategy is starting to work. Since the beginning of 2018, the percentage of people that would be categorized as pre-symptomatic in the Enroll-HD database has increased from 11% to 21%. In 2019, Enroll-HD also crossed a notable goal by collecting over 1 million aliquots of DNA, human cell lines that are available for research. There remains a large demand for high quality plasma samples for biomarker research. Therefore, the bio-sample collection is now focused on collecting high-quality plasma from 2000-3000 HD gene expansion carriers at all disease stages, but with a primary focus on pre-manifest and early manifest participants.

HDSA/CHDI FOUNDATION

HDSA and CHDI Foundation Launch HD Legacy to Promote Brain Donation for HD Research

In response to a growing need to study exactly what Huntington’s disease (HD) does to the human brain, the **HDSA** and **CHDI Foundation** announced a new collaboration in 2019 called **HD LEGACY** to support brain and other organ donations from families affected by HD who would like to make a vital contribution to research.

This new program encourages the donation of brain and other



tissues from HD gene-expansion carriers, at-risk individuals, and healthy family controls. The Harvard Brain Tissue Resource Center (HBTRC) will assist interested families throughout the process, and families will bear no costs associated with the donation.

“The decision to donate one’s body to science is an amazingly selfless act,” said Louise Vetter, President and CEO at HDSA. “Participating in HD LEGACY is truly a gift for future generations. The brains and other organs donated through this program will leave a ‘legacy’ of hope, inspiring new knowledge that will someday stop HD in its tracks.”

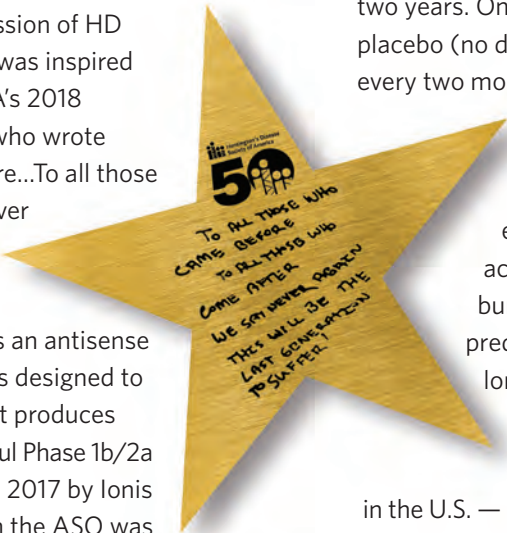
“Science still has a quite rudimentary understanding of how the human brain works,” said Robi Blumenstein, President of CHDI Management, Inc. “Researchers need more brain donations from HD-affected individuals to better understand how HD affects the human brain, what happens to the different cell types and circuits that make up the brain over time. HD LEGACY will give us new insight into how to intervene therapeutically.”

ROCHE/GENENTECH

GENERATION-HD1 Trial Completes U.S. Recruitment

The world’s first Phase 3 huntingtin-lowering drug trial is in progress. Beginning in early 2019, **Roche Pharmaceuticals** began conducting a study called **GENERATION-HD1** to understand whether their experimental therapy, RG6042, could be effective for slowing down the progression of HD symptoms. The trial’s name was inspired by a family member at HDSA’s 2018 Convention in Los Angeles, who wrote “To all those who came before...To all those who come after... We say never again! This will be the last *GENERATION* to suffer.”

This type of drug is known as an antisense oligonucleotide (ASO), and is designed to attack the RNA message that produces huntingtin protein. A successful Phase 1b/2a safety trial was completed in 2017 by Ionis Pharmaceuticals, after which the ASO was acquired by Roche (called **Genentech** in the United States). The results of that trial were published in May of 2019. The findings — no safety concerns, and successful huntingtin lowering in participants’



spinal fluid – now officially appear in the prestigious *New England Journal of Medicine*.

GENERATION-HD1

is a large trial, involving more than 100 sites around the world with

801 participants in total, all of whom will receive an intrathecal (spinal) injection every two months for two years. One third of participants will get a placebo (no drug), one third will receive RG6042 every two months, and the final third will receive the drug every four months (alternating placebo and drug).

The original trial was redesigned and expanded in 2019 to include more sites across the world and to decrease the burden on participants, based on predictions that the drug could have longer-lasting effects.

GENERATION-HD1 has already successfully recruited at all sites in the U.S. — reported by Roche to be their fastest-recruiting trial ever, due to the strength of the HD community. Because full participation takes two years and not all participants begin at once, it will likely take several years to learn whether RG6042 will be effective at slowing the symptoms of HD.



Clinical Trial Updates

WAVE LIFE SCIENCES

PRECISION-HD1 and PRECISION-HD2

Wave Life Sciences is also investigating huntingtin-lowering ASOs in two Phase 1b/2a clinical trials called **PRECISION-HD1** and **PRECISION-HD2**. Whereas the Roche drug lowers all huntingtin, Wave's approach focuses on lowering only the mutant form of huntingtin protein and leaving the healthy form intact. Participants in these early safety trials (and any future recipient of these ASOs) must have not only the HD mutation, but an additional variation in their HD gene that acts like a "genetic GPS" directing the drug to the right spot. This is true for about 70% of people with HD.

The 60 participants in each of these safety trials are receiving monthly spinal injections of either drug or placebo. The top-line results are expected in early 2020 and will include safety findings, huntingtin-lowering results, and a comparison of levels of mutant and normal huntingtin. These studies have also fully recruited in the USA.

Wave representatives spoke with families at HDSA's Convention.



UNIQURE

uniQure Initiates World's First Gene Therapy Trial of AMT-130

uniQure began recruiting for the world's first Huntington's disease gene therapy trial in the fall of 2019. The drug, called **AMT-130**, is a piece of man-made genetic code called a microRNA. It is packaged inside a type of harmless virus and delivered deep into the brain via a neurosurgery. Once the virus containing the drug enters a brain cell, it can find and chop up huntingtin RNA, so that the cell makes less toxic huntingtin protein. In theory, with only one surgical procedure, the drug will keep attacking huntingtin indefinitely. This experimental procedure has so far been successful at lowering huntingtin in animals like mice and mini-pigs.



The Phase 1/2 trial is designed to test the safety of AMT-130. 26 patients with early HD symptoms will undergo the 8-10 hour surgical procedure. Microscopic catheters will be guided to a few locations within the striatum, the deep brain regions that are most affected by HD. 16 participants will receive AMT-130, and 10 will have an imitation surgery. For 18 months after the surgery, participants will have frequent follow-up visits, with imaging, neurological exams, blood draws, and other tests to determine the safety of the drug. Then they will have yearly visits until 5 years after the surgery.

This first HD gene therapy trial is an extraordinary milestone in HD clinical research, and HDSA will continue to work closely with uniQure to provide families with up-to-date information about the progress of the study.

FURTHER UPDATES

Additional HD Drug Trials in Progress in 2019

Huntingtin-lowering is not the only tactic in the HD research arsenal. Other approaches are also being investigated, with drugs targeted to address specific symptoms or aspects of HD biology. HDSA works with industry partners to prepare family-friendly clinical trial materials, host webinars, and advertise recruiting studies through HD Trialfinder. In 2019, we received news about ongoing and new trials.

AZEVAN PHARMACEUTICALS



Azevan Pharmaceuticals

finished recruitment for the Phase 2 **STAIR Trial** of **SRX246**, a vasopressin receptor antagonist, to treat aggression and irritability in HD patients. The community should expect to hear about the results of this trial very soon.

NEUROCRINE BIOSCIENCES

In mid-November of 2019, the Huntington Study Group announced a new Phase 3 trial sponsored by **Neurocrine Biosciences**. The study, called **KINECT-HD**, will test a drug called **valbenazine**, to treat HD chorea. It will take place at 55 sites across the US and Canada.



SAGE THERAPEUTICS

Sage Therapeutics

completed recruitment of a Phase 1 safety trial of **Sage-718**, an NMDA receptor agonist, to treat cognitive changes in HD.



VACCINEX PHARMACEUTICALS

Vaccinex Pharmaceuticals

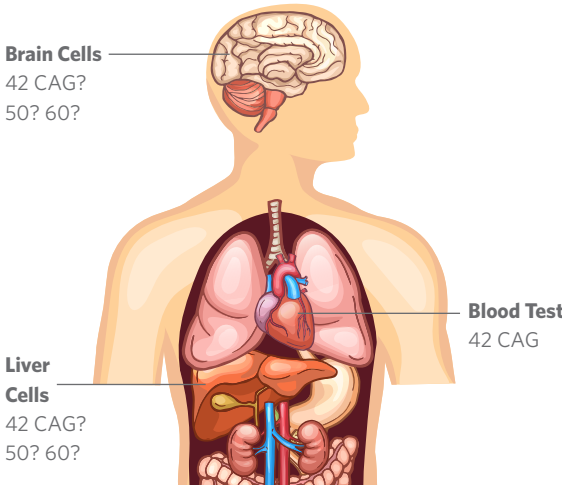
fully recruited their Phase 2 **SIGNAL Trial** of **VX15**, a semaphorin 4D antibody, to target brain inflammation in HD.



Hot Topics in HD Research

Gene Therapy

In addition to ongoing clinical trials of huntingtin-lowering ASOs in 2019, several other companies are developing drugs aimed at lowering levels of mutant huntingtin in the body and brain. These novel approaches rely on “gene therapy,” which refers to an addition, removal, or change in DNA or RNA that has the potential to treat a disease. Most gene therapy drugs being investigated for HD are viruses that will continually produce a genetic drug that can destroy the toxic huntingtin message within brain cells. Boston-based company UniQURE began a small safety trial of AMT-130, a one-time therapy that will require a brain surgery to reach areas deep in the brain that are most affected by HD. Several other companies, including Voyager, Spark, and Takeda, are working on similar approaches.



Somatic Repeat Instability

Over the past 15-20 years we have learned that the CAG repeat mutation that causes HD is dynamic — the DNA code isn’t constant, as expected, but tends to expand. This can happen from parent to child (sometimes causing juvenile HD). It can also happen throughout a person’s life in certain cells and organs, such as the liver and the area of the brain affected in HD. So a person with 42 CAG repeats could develop 50 or 60 or more repeats in some parts of the body and brain. It is believed that this expansion of CAG repeats can accelerate the onset and progression of HD, and that the body’s DNA repair machinery helps to combat this process. In 2019, new findings emerged around this topic, and the biology of repeat expansion and DNA repair is under close investigation. In 2019, HDSA funded two Human Biology Project fellows to study this topic, and the HD research foundation CHDI has directed resources towards it too. New companies were formed this year with the goal of designing drugs that could delay HD symptom onset, including Loqus23 Therapeutics and Triplet Therapeutics.

“Hiccup” in HD Gene Contributes to Age of Onset

The age that Huntington’s disease symptoms appear can vary a lot from person to person. For decades, scientists have been exploring the reasons behind this, and an important new finding has recently emerged. The vast majority of people with HD have a certain type of genetic “hiccup” near the end of their CAG repeat — one CAA. This doesn’t actually change the huntingtin protein, so we didn’t know it

was important until now. Very rarely, this CAA hiccup occurs twice (for about 1 in 100 people with HD). In these individuals, symptoms tend to occur later in life. Even more rarely, the CAA hiccup is absent (for about 1 in 300 people with HD). For these individuals, symptoms tend to occur earlier. This is the strongest genetic modifier found to date that influences HD onset. This discovery was made simultaneously by two separate research groups working with data from more than 9,000 individuals with HD, and it was formally published in August of 2019.



HDSA Research Communications

HDSA continues to provide families with the latest information about clinical trials, HD research news, and HD research activities.

Research Webinars

Research Webinars give academic and industry scientists a direct forum to share their latest findings with families.

This Week in HD Research

Dr. Leora Fox provides a roundup of HD research activities in HDSA's blog, ***This Week in HD Research***.

HDBuzz

HDSA supports **HDBuzz**, a website devoted to clear and effective communication about HD research and clinical studies.

Social Media

HDSA shares relevant scientific news on our **social media channels**.

34th Annual HDSA Convention

HDSA Convention in Boston Sets Record Attendance

The 34th Annual HDSA Convention in Boston was a great success, with the largest attendance on record (1,225 guests). Huntington's disease research had a strong presence, with talks from HDSA fellows, sessions on gene therapy, research Q&As, and representatives from biotech and pharma.

Here are some of the highlights:

The opening ceremony featured a conversation between **Dr. Marcy MacDonald**, part of the original team that discovered the HD gene, **Dr. Jang-Ho Cha**, global head of Translational Medicine in Neuroscience at Novartis, and **Cheryl Sullivan Stavelly**, HD caregiver and advocate extraordinaire.

Drs. Ed Wild and **Jeff Carroll**, HD researchers and editors of HDBuzz talked all things science with the National Youth Alliance as well as during their ever-popular "Ask a Scientist Anything" session. During Saturday's research forum they also provided a fabulous recap of the Huntington's disease research landscape in which they borrowed themes from the *Avengers: Endgame* movie to describe the important themes and pursuits in HD research right now.

Dr. Robert Pacifici, Chief Scientific Officer at CHDI, discussed how families can critically contribute to HD research.

At Saturday's research forum, HD researcher **Dr. Neil Aronin** introduced **Dr. Craig Mello**, who won the Nobel Prize for his discovery of RNAi, and **Dr. Anastasia Khvorova**, who is using RNAi

approaches to develop therapies for Huntington's disease.

Additional sessions showcased biotech companies from the Boston area working on Huntington's disease (there are many!), and company representatives spoke with families in the exhibit hall. **Roche/Genentech** and **Wave** discussed their ongoing clinical trials, and representatives from **Vybion** and **PTC Therapeutics** discussed novel huntingtin-lowering therapies in the works.

Several sessions featured HDSA Human Biology Fellows. **Dr. Wasim Malik** talked about his work on tracking eye movements to detect early movement changes in HD, while **Dr. Sophie Andrews** shared her findings that moderate exercise can be helpful for boosting memory in people with the HD gene. **Dr. Edith Pfister** reviewed current approaches to gene therapy, and 2018 Berman-Topper Fellow **Dr. Rachel Harding** spoke about the hunt for huntingtin's binding partners — which other molecules it hangs out with in our cells. Donald King research fellows **Ethan Smith**, **Jacob Friedman**, **Scott Song**, and **Wes Solem**, as well as high school student and Intel Finalist **Ritika Jeloka** presented posters on their HDSA-funded summer projects in HD laboratories.

Changing laws and rising interest in alternative treatments for HD symptoms led to this year's session on medical cannabis for Huntington's disease, in which three researchers provided an overview of the pharmacology of cannabis and discussed the limited human research from a pro/con perspective.

Finally, during the HDSA Convention, **uniQure** issued an exciting letter to the community about their clinical trial, AMT-130, to test a gene therapy for HD.

We are excited to provide an update on all the promising HD research at the 35th Annual HDSA Convention in New Orleans — see you there!



Dr. Neil Aronin introduces Dr. Anastasia Khvorova and Dr. Craig Mello at the HDSA Convention.



2019 HD Research Conferences

CAG Repeat Disorder Gordon Research Seminar & Conference

Held at the Renaissance Tuscany Il Ciocco Resort & Spa in Tuscany, Italy in June, the conference explored neurodegeneration in CAG triplet repeat diseases, from molecular pathogenesis to rational therapeutics.

Four recent HDSAs Berman-Topper HD Career Development Fellows — Dr. Tam Maiuri, Dr. Rachel Harding, Dr. Sarah Hernandez and Dr. Lauren Byrne — were on hand to present their latest research.



Huntington Study Group Annual Meeting

Seven hundred scientists, clinicians, and advocates convened in Sacramento, CA for the Huntington Study Group's annual conference. The biggest news coming out of Sacramento came from former HDSA Chairman of the Board of Trustees, Dr. Jang-Ho Cha. Dr. Cha, Global Head of Translational Neuroscience for Novartis, formally unveiled their plans to enter into the huntingtin lowering field. Novartis has identified a drug that when delivered orally can lower both the expanded and non-expanded versions of the huntingtin protein. A Phase 2 study will begin in early 2020.



Also at the HSG conference, a team from Genentech and HDSA presented a poster that provided a much needed update to the estimated prevalence of individuals with manifest HD in the United States. Based on information from a study of patient charts and accounting for the 2018 US census data; it was determined that as many as 41,000 people may have manifest HD in the US, in contrast to the frequently reported figure of 30,000 individuals. Improved estimates for the number of individuals with manifest HD has implications on policy making, planning and research prioritization.

*Dr. Tam Maiuri,
Dr. Rachel Harding,
Dr. Sarah Hernandez
and Dr. Lauren Byrne at
the 2019 CAG Repeat
Disorder Gordon Research
Seminar and Conference
in Tuscany.*

CHDI HD Therapeutics Conference

Last year's CHDI Conference was highlighted by the presentation of the data from the very first huntingtin lowering trial. This approach makes use of a drug called an antisense oligonucleotide (ASO) and the trial showed that not only does this approach appear safe, but it also lowers huntingtin protein levels in the brains of HD patients. This ASO has since moved into Phase 3 clinical trials to demonstrate efficacy. As exciting as these data were, the field is leaving no stone unturned in the quest for disease modifying therapies for HD.

The 2019 Conference was highlighted by a dedicated huntingtin lowering session to discuss the progress on other novel approaches to target the root cause of the disease. Dr. Pavlina Konstantinova from uniQure described their company's plans to initiate the first ever gene therapy trial for HD using an adeno-associated virus (AAV). The AAV will serve as a delivery device for a huntingtin lowering microRNA. This approach requires neurosurgery to carefully inject the virus expressing the drug directly into the brains of early stage HD patients. Once injected, in theory, the patient should not need to have additional injections as the AAV will continue to produce huntingtin lowering drug for the rest of their life.

Dr. Dinah Sah, CSO of Voyager, discussed a very similar approach they are undertaking in partnership with Sanofi-Genzyme. Voyager hopes to be in the clinic testing their AAV/microRNA combo in 2020.



Dr. Bev Davidson of Children's Hospital of Philadelphia (CHOP) presented allele-specific editing of the HTT gene in HD mice using a research tool called CRISPR. Finally, PTC Therapeutics discussed their innovative approach to modulate the production of the huntingtin protein using small molecules that act as RNA splicing modifiers. This would be a pill that when taken orally would get into the brain and directly modify the levels of huntingtin, thus avoiding the need for surgery or regular lumbar punctures.

Research stemming from the landmark 2015 Genome-Wide Association Study (GWAS) has generated a tremendous amount of attention from researchers. Genes, other than huntingtin, have been identified to be modifiers of the onset of HD. Many of these genes appear to be involved in the process of DNA repair. A researcher from CHDI Foundation presented their current approach to try to use these exciting data to create a novel drug that could prevent the expansion of the CAG tract that occurs over time in HD gene carriers.

One of the authors of the GWAS study and current HDSA Scientific Advisory Board member, Dr. Marcy MacDonald showed data that the true driver of the rate of pathogenesis leading to the onset of HD is the uninterrupted CAGs in a person's DNA and *not* the polyglutamine number in the protein. This is exciting because it could have large ramifications in disease staging for clinical trials and for genetic testing in the future.

HD-COPE

HD-COPE Moves into Second Year of Providing Patient and Caregiver Input to HD Drug Trial Sponsors

The Huntington's Disease Coalition for Patient Engagement (HD-COPE) was formed in late 2017 to add quality to all aspects of clinical trials through patient representative input. Patient-oriented input is critical to ensure that future HD therapies meet the needs of the patient community, speed up recruitment and decrease drop-out from clinical trials.

HD-COPE is a global coalition of the leading HD patient advocacy organizations who have united to give families affected by Huntington's disease a direct voice in HD clinical research. By expanding patient involvement beyond participation in trials as a subject, HD-COPE seeks to ensure that clinical research means research carried out 'with'



or 'by' members of the community, rather than it being 'to' or 'about' them.

HD-COPE members hail from the European Huntington's Association, Huntington's Disease Society of America, and the Huntington's Society of Canada.

In February, members of the HD-COPE traveled to New York City for their second annual training with some of the world's leading HD scientists and patient engagement thought leaders. Since its creation, input from the group remains in very high demand. Roche/Genentech, Wave Life Sciences, and Novartis all met with members of the HD-COPE team during the course of the year to help shape their clinical plans and understanding of the disease. Plans are already underway for the Third Annual HD-COPE Meeting to be held in Canada in early 2020.

At left, the HD-COPE team with Wave Life Sciences at the Second Annual HD-Cope Meeting in February in New York City.

Below, HD-COPE team members being trained on biomarkers by Dr. Ed Wild at the HD-Cope Meeting.



HDSA's Centers of Excellence

HDSA Announces Forty-Seven 2019 HDSA Centers of Excellence

In February 2019, HDSA announced that forty-seven outstanding Huntington's disease care facilities were awarded the designation of HDSA Centers of Excellence for 2019.

The 2019 HDSA Centers of Excellence program expanded to 47 Centers from 43 in 2018, and from just 20 in 2015.

The four new Centers of Excellence are: **OSF-Illinois Neurological Institute, Sanford Health (North Dakota), University of Buffalo and University of California, Irvine.** The

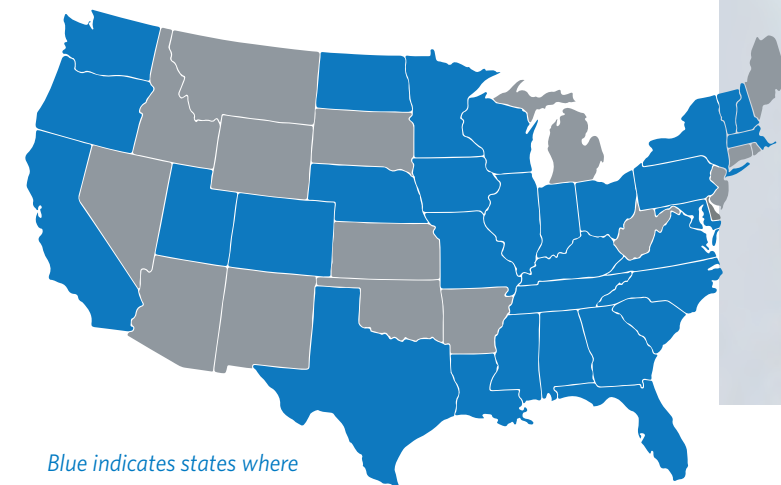
Centers of Excellence are multi-disciplinary care teams with expertise in Huntington's disease that share an exemplary commitment to bringing comprehensive care to HD families.

The strategic expansion of the Center of Excellence program allows HDSA to expand access to expert HD clinical care and clinical trial opportunities to more



families across the United States. With new Centers in North Dakota, California, Illinois and New York, we now offer care locations in 31 States plus the District of Columbia. This year, HDSA awarded a total of \$1,418,684 to the Centers of Excellence program, an increase of \$154,434 from 2018.

The HDSA Centers of Excellence provide an elite team approach to Huntington's disease care and research. Patients benefit from expert neurologists, psychiatrists, therapists, counselors and other professionals who have extensive experience working with families affected by HD and who work collaboratively to help families plan the best HD care program throughout the course of the disease. Applications to become an HDSA Center of Excellence are open to all clinics in the United States who share HDSA's commitment to high-quality, comprehensive care and access to clinical research. In short, the Centers of Excellence are the epitome of the help and hope that has guided HDSA's mission for fifty years.



Blue indicates states where HDSA Centers of Excellence are located. For a complete listing of locations, please visit HDSA.org/coe



HDSA Scientific Advisory Board

A Special Thanks to the HDSA Scientific Advisory Board

We are grateful to the Scientific Advisory Board (SAB) members who so generously donate their time and talent as volunteers! The HDSA SAB is comprised of leading experts in their fields. The role of the SAB is to

provide scientific review of research proposals to ensure that the research programs at HDSA are scientifically sound, pertinent and provide a high impact to the HD research community. Additionally, the SAB advises the HDSA Board of Trustees and management on a range of issues influencing the scientific direction of the Society.

Board Members



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Join us for the 35TH ANNUAL HDSA CONVENTION in the Big Easy at the Sheraton New Orleans Hotel.
THURSDAY, JUNE 4TH - SATURDAY, JUNE 6TH, 2020
 Three days of education, support and camaraderie!
THURSDAY
 • Exhibit Hall
 • HDSA Team Hope Walk
 • Welcome Reception
FRIDAY
 • Opening Ceremony and Keynote Address
 • Educational Workshops
 • Luncheon
 • HDSA's National Youth Alliance Talent Show
SATURDAY
 • Research Forum
 • Educational Workshops
 • HDSA Convention Gala and Awards
 For further information, please visit HDSA.org/convention



Huntington's Disease Society of America

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ABOUT HUNTINGTON'S DISEASE

Huntington's disease (HD) is a fatal genetic disorder that causes the progressive breakdown of nerve cells in the brain. It deteriorates a person's physical and mental abilities often starting in their prime working years. Currently, there is no cure for Huntington's disease.

HD is known as the quintessential family disease, because every child of a parent with HD has a 50/50 chance of inheriting the faulty gene that causes Huntington's disease. Today, there are approximately 40,000 symptomatic Americans and more than 200,000 individuals at-risk of inheriting the disease.

HUNTINGTON'S DISEASE SOCIETY OF AMERICA

The Huntington's Disease Society of America (HDSA) is the premier nonprofit organization dedicated to improving the lives of everyone affected by HD. From community services and education to advocacy and research, HDSA is the world's leader in providing help for today and hope for tomorrow for people with HD and their families.

Across the United States HDSA supports more than 50 volunteer-led Chapters and Affiliates, 47 HDSA Centers of Excellence, more than 60 social workers and 160 support groups specifically for HD families.

OUR MISSION

To improve the lives of people with Huntington's disease and their families.

OUR VISION

A world free of Huntington's disease